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JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

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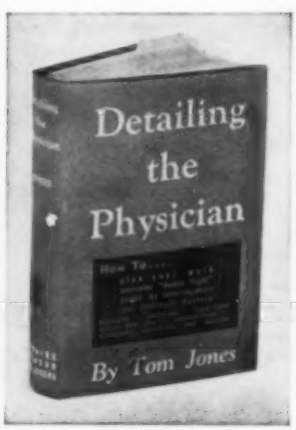

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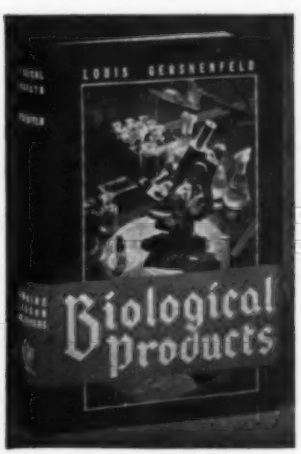

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Scientific Edition

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

A. G. DuMez, Editor, Baltimore, Maryland

Volume XXX *AUGUST, 1941* Number 8 Consecutive No. 15

Ichthyometric Studies on Some Mercurials

*By David I. Macht and Elizabeth C. Spencer**

INTRODUCTION

Fish have been employed as test objects for pharmacological work by various investigators. In fact, they are much more useful for both bioassay and for research purposes than most pharmacologists appreciate. Larger fish have been employed for the study of drugs on the circulation in the gills and the effect of various chemicals on the heart. It is the small fish, however, which are especially useful for testing the toxic effect of drugs on different physiological functions. Thus, small fish have been used advantageously for the study of local anesthetics (1), for the assay of picrotoxin (2), for testing the potency of digitalis (3) and for the detection of estrogenic (4) and androgenic hormones (5). Recently, goldfish have been recommended for the bioassay of thyrotropic hormone (6) and also for the study of the biophysical effects of x-rays (7). Macht with Craig used goldfish in a comparative study of nicotine derivatives (8) and with Leach employed them also for quantitative comparison of a long series of isomeric octyl alcohols (9). In connection with the last-named research, a graphic method for recording the activity of goldfish in solutions of various drugs was described. The present writers have employed the same ichthyometric technique in studying the effects of opium alkaloids, snake venoms and numerous other drugs. The results of this investigation will be published in due time. In the following paper the authors describe their study by this quantitative ichthyometric method of the toxicity of a series of mercury compounds, the results of which are of both scientific and practical interest.

EXPERIMENTAL

Technique.—The writers studied the behavior of goldfish (*Carassius auratus*) with an ichthyometer registering their movements on a slowly revolving kymograph. Figure 1 is an outline of the simple apparatus, a modification of the ichthyometer originally described by Spencer in 1929 (10). The set-up consists of a round granite or enamel bowl filled with water to a depth of one and a half to two inches. Two crossed metal springs are so placed over the top that the hole made at their point of juncture is directly over the center of the bowl. Goldfish approximately two inches in length from snout to root of tail are used for these tests. A silk thread is drawn through the muscle just in front of the dorsal

* From the Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc., Baltimore, Md.

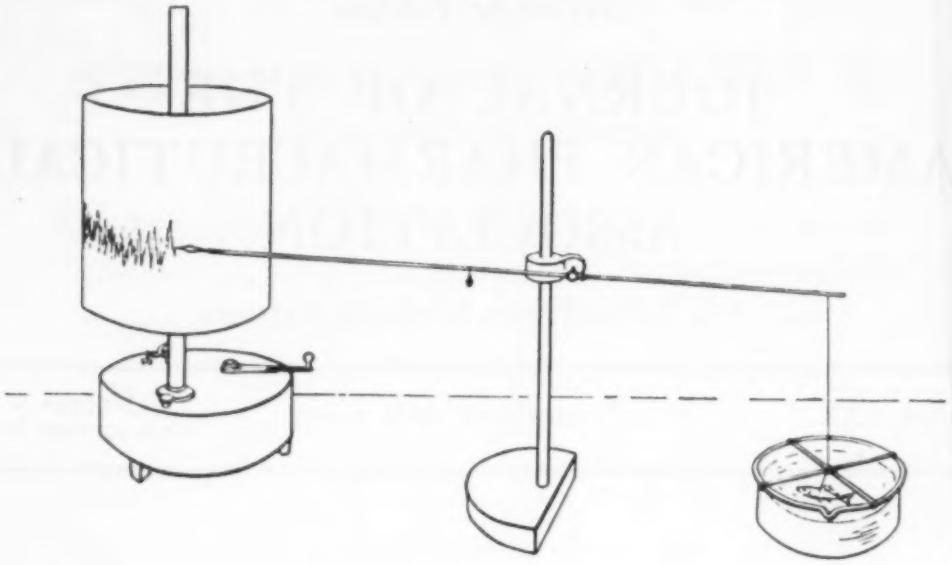

Fig. 1.—Ichthyometer.

fin and tied in a short loop, the other end being passed through the opening made where the bars cross and secured to one arm of a long lever. The other arm is lightly weighted to balance the two arms on the pivot and the fish's movements result in the weaving of a pattern on the slowly revolving kymograph. The length of the lever arm is adjusted, so that the stylus records on the drum not only the frequency but also the amplitude of lever contractions. The shallow water in the round bowl renders the vertical or diving movements of the fish negligible while its motions in horizontal directions are fully recorded.

This apparatus can be employed for study of the behavior of fish under the influence of any kind of drug or chemical, whether sedative or convulsant. When necessary, the fish can be screened from light by blotters placed over the top of the bowl. When studying the normal movements of the suspended goldfish as well as their behavior while under the influence of various drugs, the authors place in the bowl a second fish as companion to that recording its contractions. Quiescent periods may thus be effectually eliminated and the effect of the drug used can be studied on the unencumbered goldfish as well as on that harnessed to the lever.

Effect of Various Mercurials.—A number of mercury compounds—*i. e.*, mercuric chloride, mercuric cyanide, mercurochrome or dibrom-oxy-mercuri fluorescein, merodicein or mono-hydroxy-mercuri-diiodo resorcinsulphonphthalein, and flumerin or oxy-mercuri fluorescein—were thus studied on goldfish; and the results obtained were extremely interesting. It was found that the organic and inorganic mercury derivatives varied greatly in their toxicity for fish. The three organic compounds, mercurochrome, merodicein and flumerin, all proved to be relatively little toxic for goldfish. Thus, for instance, 1:10,000 solutions of mercurochrome were usually innocuous and goldfish placed therein survived for 24 hours. Even when placed in solutions as strong as 1:5000 of mercurochrome, the goldfish survived from 12 to 15 hours. Identical results were obtained with solutions of flumerin and merodicein. Very different, on the contrary, were the effects of inorganic mercurials, very dilute solutions of which soon proved toxic for goldfish. Healthy specimens, placed in 1:100,000 solutions of mercuric chloride, died in a few hours. Even 1:200,000 dilutions of bichloride were fatal for these fish. Solutions of mercuric cyanide, of course, were more toxic for goldfish.

Of greater interest were the results obtained with combinations or mixtures of an organic with an an inorganic mercurial. In special studies made with a combination of mercurochrome and bichloride of mercury minute traces of the latter potentiated the toxicity of the mercurochrome solution, *i. e.*, effected a synergism, indicated by heightened toxicity of the *mixture* as compared with that of the individual constituents. The activity of goldfish placed in such solutions was speedily inhibited and death followed. Such a difference in behavior of goldfish in solutions of pure mercurochrome and of mercurochrome containing traces of inorganic mercury salts, respectively, obviously suggests a delicate biological method for discovering impurities in oxy-mercuri-dibrom fluorescein and also the spurious preparations of mercurochrome occasionally foisted on the market.

The subjoined ichthyograms or tracings made by goldfish placed in the various solutions described above strikingly illustrate the results obtained. In each case the upper curve was traced on a kymo-

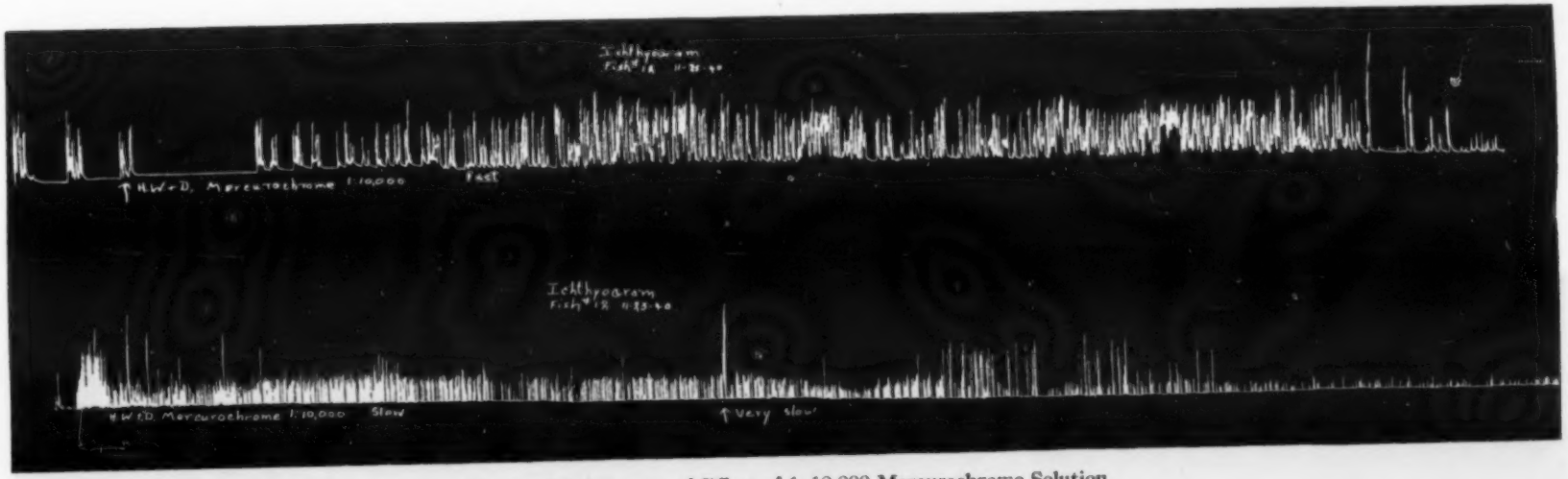

Fig. 2.—Ichthyogram of Effect of 1:10,000 Mercurochrome Solution.

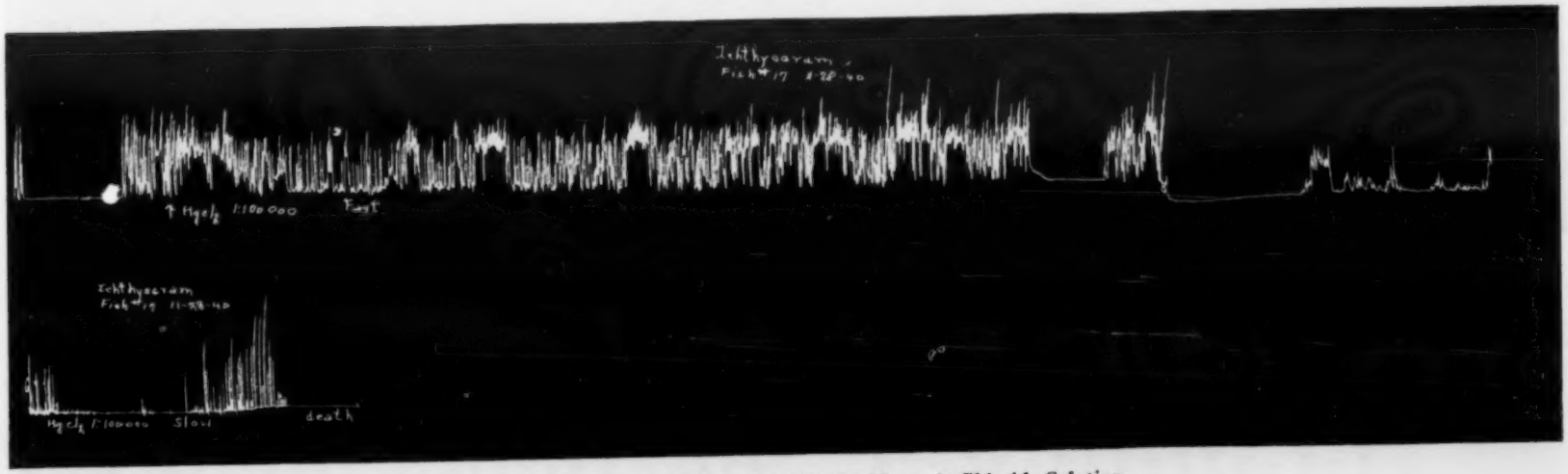

Fig. 3.—Ichthyogram of Effect of 1:100,000 Mercuric Chloride Solution.

Fig. 4.—Ichthyogram of Effect of a Mixture of 1:10,000 Mercurochrome Solution and 1:100,000 Mercuric Chloride Solution.

graph making one revolution an hour whereas the lower was made on a much slower drum running overnight. Figure 2 is an ichthyogram produced by a goldfish placed in a 1:10,000 solution of mercurochrome (H., W. & D.) and surviving for 24 hours. Figure 3 shows the effect of a dilute solution of mercuric chloride (1:100,000), which caused death in a few hours. Figure 4 reveals the results obtained with a solution containing a mixture of mercurochrome, 1:10,000, and bichloride of mercury, 1:100,000.

SUMMARY

1. A simple method for graphically recording on the kymograph the neuromuscular activity and general behavior of small fish has been described.

2. This method has been employed by the authors for pharmacological study of the comparative effects of various drugs on goldfish.

3. A striking difference was noted in the ichthyograms produced by goldfish placed, respectively, in solutions of certain organic mercurials and of inorganic mercury salts, the former being much less toxic than the latter.

4. The ichthyometric method has proved useful not only in differentiating between organic and inorganic mercury compounds but also in discovering the presence of inorganic mercury contaminants in mercurochrome.

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"To be guided by reason is to obey the laws of nature."—Ernest Wood

Non-Toxic Character of Ursolic Acid.*

Preliminary Study

By J. A. Lubitz and C. R. Fellers†

INTRODUCTION AND REVIEW OF LITERATURE

Ursolic acid is a monohydroxytriterpene acid (1) of the formula $C_{30}H_{48}O_3$ (2). It is widely distributed in nature, having been found in *uva ursi* leaves (3), mistletoe (4) and the skins of apples (5), pears (6) and cherries (7). Cranberry pomace obtained in the commercial canning of cranberry sauce was also found to contain ursolic acid (8). According to Winterstein and Stein (9), ursolic acid in the form of a saturated solution of its sodium salt is toxic to fish. This reported toxicity to fish might be due to the use of a saturated solution or possibly to still other factors. As ursolic acid is being introduced as an emulsifying agent in pharmaceutical and food preparations, it was thought advisable to determine whether or not it possessed toxic properties.

EXPERIMENTAL

Description of Sample.—The ursolic acid used in this study was prepared from cranberry skins.[1] This ursolic acid was a fairly pure sample although it had not been crystallized from alcohol. The yield of ursolic acid manufactured from dried cranberry skins is about 10 per cent.

Toxicity.—Rats, guinea pigs, chickens and rabbits were fed ursolic acid orally at levels of from 1000 to 5000 mg. per Kg. of body weight. These animals were placed in individual cages with abundant drinking water, but were left without food for 24 hours. The ursolic acid was then fed mixed with dried bread crumbs in the case of the rats and guinea pigs, laying mash in the case of the chickens and Purina Fox Chow (a prepared dry feed) in the case of the rabbits. The animals were observed for 12 days during which time no toxic manifestations were noted. Autopsies were then performed on a representative number of animals. No abnormalities were evident; therefore, it would seem that ursolic acid is not injurious to these animals when fed orally in large quantity. The liver, kidneys, heart, lungs, adrenals, stomach, intestinal tract and ovaries (in the case of females) were carefully examined

---

* Contribution No. 409, Massachusetts Agricultural Experiment Station, Amherst.

† Nutrition Laboratory, Massachusetts State College.

[1] Ursolic acid obtained through the courtesy of Cranberry Canners, Inc., South Hanson, Mass.

microscopically and while a histological study was not made, gross microscopic examination showed no differences from normal tissue.

Each of three adult male subjects was given ursolic acid orally in doses of 0.5 Gm. daily (20 mg. per Kg. body weight) over a 3-day period. No symptoms or discomfort of any kind were noted. We may conclude, consequently, that ursolic acid in moderate amounts is innocuous to humans.

SUMMARY

1. According to the literature (9) ursolic acid in a saturated solution of its sodium salt is toxic to fish.

2. Ursolic acid was found to be non-toxic to rats, guinea pigs, chickens, rabbits and humans.

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A Colorimetric Method for the Assay of Diethylstilbestrol*

By Earl B. Dechene, B.Sc.

Various methods have been described in the literature (1, 2, 3) for the quantitative estimation of diethylstilbestrol. These methods have the disadvantage of a narrow range of applicability, or they require apparatus not generally available in control laboratories. An attempt was therefore made to devise a colorimetric method which would be applicable to the estimation of relatively small amounts of diethylstilbestrol present in pharmaceutical preparations.

* From The Research Laboratories, Charles E. Frosst & Co., Montreal, P. Q.

It was found that the xanthoproteic reaction was suitable for this purpose and in this paper is presented a method which is simple, rapid and accurate, for the estimation of diethylstilbestrol in tablet, ampul and suppository preparations.

It should be emphasized that the method to be described is applicable only to those preparations in which diethylstilbestrol is the only phenyl derivative present.

EXPERIMENTAL

The Color Test.—Transfer an aliquot of a methanol solution of pure diethylstilbestrol to a test-tube graduated at 16 cc. Remove the methanol in a boiling water bath with the aid of vacuum. To the residue add 0.75 cc. of concentrated nitric acid (sp. gr. 1.42) and place the tube in a boiling water bath for ten minutes. Cool the tube to room temperature and add 4 cc. of 10% ammonium hydroxide. Cool again to room temperature and dilute to 16 cc. with water.

Experiments showed that the color produced by the reaction was stable over long periods of time and was unaffected by various concentrations of reagents over a wide range. The 10-minute period of heating was found to ensure maximum color development.

Using this method on amounts from 0.25 mg. to 1.75 mg. of diethylstilbestrol the yellow colors produced were found to be linear functions of the concentrations of diethylstilbestrol present when measured in a B. & L. Duboscq Colorimeter.

Attention was next turned to the effect on the color reaction of those substances commonly used as tablet excipients, *e. g.*, starch, lactose, acacia, magnesium stearate, calcium phosphate. It was found that when a methanol extract of various known amounts of diethylstilbestrol was made in the presence of a proportionate amount of a mixture of these excipients and compared with a methanol solution of 0.5 mg. diethylstilbestrol as standard, practically quantitative results were obtained.

The following procedure was therefore applied to the assay of tablets.

Weigh a number of tablets equal to 5 mg. to 10 mg. of diethylstilbestrol and determine the average weight of one tablet. Powder the tablets and take a weight of the powder equal to approximately 5 mg. of diethylstilbestrol. Macerate the powder in 10 cc. of methanol for 15 minutes with the aid of a glass rod. Filter and transfer an aliquot equal to 0.5 mg. of diethylstilbestrol to a test-tube graduated at 16 cc. Treat as described under Color Test, and compare the color to that given by 0.5 mg. of a standard prepared in the same way.

Using this method in a considerable number of assays on carefully prepared tablets an average deviation of $\pm 1\%$ was obtained with a maximum deviation of $\pm 5\%$ in only two instances.

Table I.—Comparison of the Effect of Tablet Excipients

Sample[a]	Standard, Mg.	Control Reading	Sample[b] Reading	Theoretical, Mg.	Found, Mg.	Recovery, %
1	0.5	20.0	10.0	1.00	1.00	100
2	0.5	20.0	13.26	0.75	0.754	100.5
3	0.5	20.0	20.18	0.50	0.497	99.5
4	0.5	20.0	29.92	0.25	0.251	100.5

[a] Each sample contained 65 mg. of excipient mixture.
[b] The sample readings shown are the average of 5 readings.

Assay Method for Solutions of Diethylstilbestrol in Oil.—Solutions of this nature are usually prepared by dissolving the diethylstilbestrol in a vegetable oil such as sesame oil.

For experimental purposes such a solution was prepared by dissolving 50 mg. of diethylstilbestrol in 50 cc. of sesame oil. Different methods of extraction were tried and the following one was found to give quantitative results.

Place sufficient of the oil to give approximately 5 mg. of diethylstilbestrol in a small separatory funnel and add 30 cc. of light petroleum ether. Extract three times with $N/1$ sodium hydroxide, using 15 cc., 10 cc., 10 cc. Combine the alkaline extracts, acidify with 10% sulfuric acid and extract three times with ether, using 20 cc., 15 cc., 10 cc. Combine the ether extracts and evaporate to dryness. Dissolve the residue in 10 cc. of methanol and apply the color reaction to an aliquot representing 0.5 mg. of diethylstilbestrol as described under Color Test.

Results obtained with this method showed an average deviation of $\pm 1\%$.

Assay Method for Suppositories of Diethylstilbestrol.—The suppositories used in these experiments were of the glycerine-gelatine type. Several methods of extraction were tried and finally the following one was used.

Place a number of suppositories equal to approximately 5 mg. of diethylstilbestrol in a separatory funnel, add 50 cc. of hot water and agitate until dissolved. Cool and extract three times with ether using 20 cc., 15 cc., 10 cc. Combine ether extracts and extract twice with 15 cc. of $N/1$ sodium hydroxide. Acidify the combined alkaline extracts with 10% sulfuric acid and extract three times with ether using 15 cc., 10 cc., 10 cc. Combine the ether extracts and evaporate to dryness. Dissolve the residue in 10 cc. of methanol and take an aliquot equal to 0.5 mg. of diethylstilbestrol and treat as described under the Color Test.

Results obtained with this method showed deviations of 5%.

SUMMARY

A color reaction for the quantitative estimation of diethylstilbestrol in tablets, ampuls and suppositories has been described.

This reaction is not specific; it is applicable to preparations in which stilbestrol is known to be the only phenyl derivative present.

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A Critical Study of the Physico-Chemical Properties of Tyrolean Oil *Pinus Pumilio* Haenke (Oil *Pinus Montana* Miller) Fam. Pinaceae and Oil *Abies Alba* Miller (Oil *Abies Pectinata* D. C.) Fam. Pinaceae*

By Charles H. Grimm† Edward E. Langenau† and Ernest S. Guenther‡

During recent years, the properties of shipments of guaranteed purity of Oil *Pinus Pumilio* Haenke (Oil *Pinus Montana* Miller) (Fam. *Pinaceæ*) and Oil *Abies Alba* Miller (Oil *Abies Pectinata* D. C.) (Fam. *Pinaceæ*) received from the Tyrol were found to differ considerably from the limits set forth by the standard accepted literature (1) and in the case of Oil *Pinus Pumilio* (Oil of Dwarf Pine Needles) from the standards of the United States Pharmacopœia. This research was undertaken to study the physical and chemical properties of authentic samples of Oil *Pinus Pumilio* and Oil *Abies Alba* from the Tyrol which were distilled under the instruction of our Research Department in different locations, at different times and under different conditions of weather, plant material, etc.

* Contribution from the Research Laboratories of Fritzsche Brothers, Inc., N. Y.
† Research Chemist.
‡ Vice-President, Chief Research Chemist.

E. S. Guenther, in 1936, in his survey of Tyrolean oils (2) first pointed out that a change from the reported literature had occurred in the boiling ranges of Oil *Pinus Pumilio* and Oil *Abies Alba*. Schimmel & Co. in their *Annual Reports* (3) mentioned that they had noticed no such change as regards Oil *Abies Alba* and commented, "if 40% of such an oil passes over below 170° C. it has probably been adulterated with Turpentine Oil." The results of the following investigation show definitely that a change in the boiling range of genuine oils has actually occurred.

EXPERIMENTAL

A. Methods.—The samples of Oil *Pinus Pumilio* and Oil *Abies Alba* were examined using the following methods and procedures:

Specific Gravity was determined in a 10-cc. conical pycnometer with a ground-in thermometer. In the case of Oil *Pinus Pumilio*, the gravities are given at 25° C./25° C. since this oil is official in the U. S. P. XI. For Oil *Abies Alba*, the gravities are given at 15° C./15° C. in accord with most scientific work on essential oils.

Optical Rotation was determined in a 100-mm. tube with a Schmidt and Hansch half-shadow polarimeter using a monochromatic sodium vapor lamp as a light source. The rotations for Oil *Pinus Pumilio* were determined at 25° C.; for Oil *Abies Alba*, at 20° C.

Solubility was determined in a 10-cc. glass-stoppered cylinder. The temperature was adjusted to 25° C. for Oil *Pinus Pumilio* and to 20° C. for Oil *Abies Alba* by immersion in a water bath of suitable temperature.

Refractive Index was determined with an Abbé type refractometer. All readings were made at 20° C.

Acid Value was determined with a 5-Gm. sample dissolved in Alcohol and titrated with 0.1*N* NaOH.

Ester Content was determined using a 5-Gm. sample and 0.5*N* NaOH. Refluxing on a steam bath was continued exactly 1 hour; the flask was then permitted to cool for 15 minutes before titrating with 0.5*N* HCl. Esters were calculated as Bornyl Acetate.

Total Alcohol Content was determined by acetylation (1 hour) with subsequent saponification. Total alcohols were calculated as Borneol using the following formula:

$$\text{Total Borneol} = \frac{A \times 7.71}{B - (A \times 0.021)} \times (1 - (E \times 0.0021))$$

where A = cc. of 0.5*N* NaOH consumed
B = weight of acetylized oil (in grams)
E = percentage of ester, calculated as Bornyl Acetate

Table I.—Conditions of Distillation of Oil *Pinus Pumilio*, Haenke (Fam. Pinaceæ)

Sample	General Climatic Condition	Soil	Approx. Age of Tree	Yield of Oil, %	Distillation Material
1	Sunny	Stony	Old	0.24	Needles only—dry
2	Sunny	Stony	Old	0.29	Branch tops with needles (cut to 1 cm.)—dry
3	Sunny	Stony	Old	0.29	Branch tops with needles (cut to 1 cm.)—dry
4	Sunny	Stony	Young	0.36	Wood (branches of 3 cm. diameter cut to 1 cm. *without* needles)—dry
5	Sunny	Stony	Young	0.23	Needles only—dry
6	Sunny	Stony	Old	0.37	Wood (branches of 3 cm. diameter cut to 1 cm. *without* needles)—wet
7	Sunny	Stony	Old	0.34	Small branches with needles
8	Sunny	Stony	Old	0.36	Small branches with needles
9	Sunny	Stony	Old	0.30	Needles only
10	Sunny	Gravel	Old	0.29	Small branches with needles
11	Sunny	Gravel	Young	0.29	Small branches with needles
12	Sunny	Gravel	Young	0.30	Small branches with needles
13	Sunny	Gravel	Old	0.31	Small branches with needles
14	Sunny	Gravel	Old	0.29	Small branches with needles
15	Sunny	Gravel	Old	0.29	Small branches with needles
16	Sunny	Stony	Young	0.28	Small branches with needles
17	Sunny	Stony	Young	0.30	Small branches with needles
18	Sunny	Stony	Old	0.23	Small branches with needles
19	Shady	Stony	Old	0.25	Needles only—dry
20	Shady	Stony	Old	0.27	Branch tops with needles—dry
21	Shady	Stony	Old	0.25	Branch tops with needles—dry
22	Shady	Gravel	Young	0.26	Branch tops with needles—dry
23	Shady	Gravel	Young	0.28	Branch tops with needles—dry
24	Shady	Gravel	Young	0.27	Branch tops with needles—dry

Note: All samples were distilled from trees growing in the Tyrol region at an altitude of approximately 1800 meters. The distillations were continued for 5 hours, the average pressure in the still being 0.3 atmosphere above normal.

Table II.—Properties of Oil *Pinus Pumilio*, Haenke (Fam. Pinaceæ)

Sample	D. 25° C.	α_D 25° C.	n_D 20° C.	Solubility 25° C.	Acid Value	Ester (as Bornyl Acetate), %	Total Alcohol (as Borneol), %	Aldehyde (as Caproic), %
1	0.856	−12° 25′	1.4778	Hazy up to 10 vols. 90% alc.	0.7	4.1	5.0	0.27
2	0.857	− 9° 13′	1.4768	Hazy up to 10 vols. 90% alc.	0.8	4.1	5.2	0.29
3	0.864	− 6° 23′	1.4780	8 vols. 90% alc. A.M.	0.7	5.2	8.0	0.12
4	0.856	−13° 33′	1.4776	Hazy up to 10 vols. 90% alc.	0.8	4.4	4.8	0.01
5	0.864	− 5° 38′	1.4780	6.5 vols. 90% alc. A.M.	0.6	5.7	6.4	0.01
6	0.864	− 6° 52′	1.4779	5.5 vols. 90% alc. A.M.	0.9	5.5	6.1	0.16
7	0.861	−11° 15′	1.4775	Hazy up to 10 vols. 90% alc.	1.1	7.2	8.7	0.31
8	0.862	− 3° 47′	1.4787	Hazy up to 10 vols. 90% alc.	0.4	4.8	5.5	0.14
9	0.858	−14° 6′	1.4769	Hazy up to 10 vols. 90% alc.	0.7	5.9	8.0	0.12
10	0.871	−10° 45′	1.4766	Hazy up to 10 vols. 90% alc.	0.9	9.5	9.3	0.40
11	0.860	−12° 46′	1.4790	Hazy up to 10 vols. 90% alc.	1.3	4.4	5.0	0.17
12	0.862	− 8° 13′	1.4784	Hazy up to 10 vols. 90% alc.	0.5	4.7	4.2	0.15
13	0.862	−10° 4′	1.4781	Hazy up to 10 vols. 90% alc.	0.5	4.1	5.5	0.06
14	0.860	− 6° 5′	1.4779	Hazy up to 10 vols. 90% alc.	0.4	3.9	5.1	0.19
15	0.861	−13° 1′	1.4750	Hazy up to 10 vols. 90% alc.	0.2	3.3	6.7	0.47
16	0.862	− 3° 19′	1.4786	Hazy up to 10 vols. 90% alc.	0.2	4.1	5.6	0.02
17	0.862	− 7° 4′	1.4760	Hazy up to 10 vols. 90% alc.	0.3	4.2	10.3	0.17
18	0.857	−12° 30′	1.4769	Hazy up to 10 vols. 90% alc.	1.0	6.5	8.6	0.09
19	0.854	−13° 2′	1.4770	Hazy up to 10 vols. 90% alc.	0.9	4.7	9.1	0.24
20	0.856	−13° 46′	1.4770	Hazy up to 10 vols. 90% alc.	0.8	5.8	6.8	0.09
21	0.857	−13° 29′	1.4766	Hazy up to 10 vols. 90% alcs.	0.8	6.0	6.7	0.17
22	0.858	−12° 17′	1.4768	Hazy up to 10 vols. 90% alc.	0.7	6.2	7.9	0.16
23	0.857	−15° 16′	1.4766	Hazy up to 10 vols. 90% alc.	0.9	5.9	7.3	0.16
24	0.855	−15° 5′	1.4769	Hazy up to 10 vols. 90% alc.	0.9	5.4	7.2	0.23

Aldehyde Content for Oil *Pinus Pumilio* was determined by means of 0.5 *N* Hydroxyamine Hydrochloride Solution using Brom Phenol Blue indicator. Titration of the liberated HCl after 30 minutes was made with 0.1*N* NaOH. Aldehyde was calculated as caproic aldehyde.

Boiling Range was determined by carefully distilling a 50-cc. sample of the oil in a four-bulb Ladenburg flask (diameter of main bulb = 70 mm., of first refluxing bulb = 45 mm., of second refluxing bulb = 40 mm., of third refluxing bulb = 35 mm.). Anschutz thermometers were used throughout, obviating any stem corrections. Distillations were carried out at atmospheric pressure.

Odor Comparisons were made with standard authentic type samples.

B. Results.—The conditions of distillation, the analyses and the fractionations of twenty-four samples of Oil *Pinus Pumilio* are given in Tables I, II and III.

The conditions of distillation, the analyses and the fractionations of fifteen samples of Oil *Abies Alba* are given in Tables IV, V and VI.

C. Discussion of Results.—Oil of *Pinus Pumilio.* For the sake of comparisons and in order to present a clearer picture of our data, the limits of the standard literature are given in Table VII. It may be seen from our analyses of genuine oils that many of these Tyrolean oils failed to meet the limits as outlined in the literature.

As to the limits of Gildemeister and Hoffmann, "Die Ätherischen Öle," Sample 10 failed to comply with the requirement for specific gravity; Samples 8 and 16, the requirement for optical rotation; Samples 7 and 11, the requirement for acid value; Sample 10, the requirement for ester content; and

Table III.—Boiling Ranges of Oil *Pinus Pumilio*, Haenke (Fam. Pinaceæ)

Sample	Up to +160° C., %	+160°–165° C., %	+165°–170° C., %	+170°–175° C., %	+175°–180° C., %	+180°–185° C., %	+185°–190° C., %	+190°–195° C., %	+195°–200° C., %	+200°–205° C., %	+205° C. and Up, %
1	3.8	5.2	21.2	28.0	18.8	4.4	1.2	0.4	0.8	0.8	15.4
2	4.4	4.0	34.4	28.4	8.0	4.4	0.8	0.6	2.0	1.4	11.6
3	0.4	3.8	18.0	24.4	16.8	9.6	2.4	4.4	1.8	3.2	15.2
4	1.2	2.0	20.2	30.4	12.0	8.4	6.2	1.8	2.2	1.8	13.8
5	2.8	1.2	9.2	32.4	18.4	9.6	4.0	4.4	0.4	2.2	15.4
6	3.6	4.2	12.2	24.0	17.8	7.4	5.4	4.2	1.8	0.6	18.8
7	2.4	7.0	21.0	25.6	9.6	4.4	3.2	5.6	3.2	2.4	15.6
8	3.8	0.8	12.8	34.8	17.2	8.4	4.0	1.6	0.8	0.8	15.0
9	3.6	5.2	18.4	30.0	10.8	4.4	3.2	6.0	1.6	2.4	14.4
10	2.0	6.4	18.6	23.2	17.8	5.2	4.0	3.2	2.4	2.0	15.2
11	3.2	4.4	12.0	37.6	7.2	4.4	6.4	4.8	2.4	0.4	0.4
12	1.8	3.8	17.2	26.4	18.8	7.2	4.0	1.6	3.2	2.0	14.0
13	0.4	2.0	12.2	36.0	22.0	6.8	2.2	1.8	0.8	0.6	15.2
14	3.0	3.4	18.4	32.8	15.2	6.4	4.4	2.8	0.8	0.8	12.0
15	5.0	17.4	30.8	18.4	5.4	4.4	6.0	1.2	2.0	0.4	9.0
16	3.2	4.0	16.0	25.6	24.0	8.4	3.6	2.0	0.6	0.2	12.4
17	4.0	5.8	24.0	26.4	8.0	8.0	4.4	0.8	3.6	0.2	14.8
18	0.4	2.0	13.4	22.6	14.0	6.2	6.4	5.8	6.4	4.0	18.8
19	4.0	3.5	24.8	28.8	12.4	6.4	2.4	4.0	0.7	0.6	12.4
20	1.6	3.2	22.4	25.2	19.2	4.8	3.2	2.4	0.4	4.0	13.6
21	2.6	3.0	18.8	30.4	14.8	8.4	6.0	0.4	0.6	1.8	13.2
22	2.0	4.4	21.2	22.4	12.2	4.2	8.9	2.2	0.6	1.2	20.7
23	1.5	7.0	34.0	14.0	10.0	6.4	2.4	2.4	1.2	0.8	20.3
24	3.2	6.0	26.0	24.8	15.6	6.4	2.8	2.0	0.8	2.6	9.8

Table IV.—Conditions of Distillation of Oil *Abies Alba*, Miller (Fam. Pinaceæ)

Sample	General Climatic Condition	Soil	Approx. Age of Tree	Yield of Oil, %	Distillation Material
1	Sunny	Gravel	Young	0.32	Branch tops with needles (cut to 1/2 cm.)—dry
2	Sunny	Gravel	Young	0.10	Wood (branches of 2 cm. diameter cut to 2 cm. *without* needles)
3	Sunny	Gravel	Young	0.27	Branch tops with needles (cut to 1/2 cm.)—dry
4	Sunny	Gravel	Old	0.30	Needles only—dry
5	Sunny	Gravel	Old	0.27	Branch tops with needles (cut to 1 cm.)—dry
6	Shady	Stony	Old	0.10	Wood (branches of 2 cm. diameter cut to 2 cm. *without* needles)
7	Sunny	Stony	Old	0.27	Branch tops with needles (cut to 1 cm.)—dry
8	Shady	Stony	Old	0.30	Needles only
9	Shady	Stony	Old	0.16	Bark only (cut to 1 1/2 cm.)
10	Shady	Damp	Old	0.30	Branch tops with needles (cut to 1/2 cm.)—dry
11	Shady	Damp	Old	0.15	Wood (branches of 3 cm. cut to 1/2 cm. *without* needles)
12	Shady	Damp	Old	0.38	Branch tops with needles (cut to 1/2 cm.)—dry
13	Shady	Damp	Old	0.30	Needles only—dry
14	Shady	Damp	Old	0.15	Bark only (cut to 1/2 cm.)
15	Shady	Damp	Old	0.12	Wood (branches of 3 cm. cut to 1/2 cm. *without* needles)

Note: All samples were distilled in the Tyrol region within two weeks after date of felling. Trees growing at an altitude of 480–850 meters were used. All distillations were continued for 5 hours, the average pressure in the still being 0.5 atmosphere above normal.

all samples, the requirement for boiling range. However, all these samples met the requirements for refractive index and for solubility. Of these twenty-four oils, none met all the requirements set forth by Gildemeister and Hoffmann.

As to the limits of the U. S. P. X, Sample 10 failed to comply with the requirement for specific gravity; Samples 1, 2, 4, 7, 8, 9, 10, 11, 13, 15, 16, 18, 19, 20, 21, 22, 23 and 24, the requirement for optical rotation; Sample 1, 2, 4, 8, 11, 12, 13, 14, 15, 16, 17 and 19, the requirement for ester content; all samples failed to meet the requirement for solubility and boiling range. However, all these samples met the requirement for refractive index. Of these twenty-four oils, none met all the requirements set forth by U. S. P. X.

As to the limits of the U. S. P. XI, Sample 10 failed to comply with the requirement for specific gravity; Samples 1, 4, 8, 9, 11, 15, 16, 18, 19, 20, 21, 22, 23 and 24, the requirement for optical rotation; Samples 1, 2, 4, 8, 11, 12, 13, 14, 15, 16, 17 and 19, the requirement for ester content; Samples 1, 2, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, the requirement for solubility; Sample 15, the requirement for boiling range. Of these twenty-four oils only Samples 3, 5 and 6 met all the requirements set forth by the U. S. P. XI.

As a matter of interest the analyses of shipments (4) of Tyrolean Oil *Pinus Pumilio* received in the last few years are presented in Table VIII.

The U. S. P. X requires a solubility of Oil *Pinus Pumilio* in ten parts of 80% alcohol. Genuine

Table V.—Properties of Oil *Abies Alba*, Miller (Fam. Pinaceæ)

Sample	D. 15° C.	α_D 20° C.	n_D 20° C.	Solubility 20° C.	Acid Value	Ester (as Bornyl Acetate), %	Total Alcohol (as Borneol), %
1	0.874	−47° 36′	1.4740	5.5 vols. 90% alc. A.M.	0.7	6.4	6.7
2	0.874	−28° 35′	1.4751	5.5 vols. 90% alc. A.M.	0.4	4.1	5.5
3	0.877	−46° 35′	1.4742	5.5 vols. 90% alc. A.M.	0.4	8.1	8.0
4	0.880	−47° 4′	1.4745	5 vols. 90% alc. A.M.	0.9	7.1	8.3
5	0.876	−41° 52′	1.4746	5 vols. 90% alc. A.M.	0.9	5.6	9.1
6	0.877	−29° 1′	1.4760	6 vols. 90% alc. A.M.	1.3	0.8	3.6
7	0.879	−43° 47′	1.4749	5 vols. 90% alc. A.M.	0.7	7.6	7.7
8	0.879	−47° 51′	1.4739	5 vols. 90% alc. A.M.	0.3	8.6	8.6
9	0.875	+ 9° 30′	1.4720	5 vols. 90% alc. A.M.	0.2	1.6	3.0
10	0.867	−54° 56′	1.4733	6 vols. 90% alc. A.M.	0.2	3.0	13.4
11	0.867	−58° 12′	1.4751	6 vols. 90% alc. A.M.	0.6	2.3	3.2
12	0.867	−66° 37′	1.4740	6 vols. 90% alc. A.M.	0.3	3.3	6.2
13	0.870	−54° 56′	1.4741	6 vols. 90% alc. A.M.	0.7	2.8	4.3
14	0.878	+ 9° 29′	1.4740	5 vols. 90% alc. A.M.	1.1	0.2	3.3
15	0.870	−13° 30′	1.4760	Hazy up to 10 vols. 90% alc.	1.2	8.2	8.7

Table VI.—Boiling Ranges of Oil *Abies Alba*, Miller (Fam. Pinaceæ)

Sample	Up to +165° C., %	+165°–170° C., %	+170°–175° C., %	+175°–180° C., %	+180°–185° C., %	+185°–190° C., %	+190°–195° C., %	+195°–200° C., %	+200°–205° C., %	+205° C. and up, %
1	23.0	26.0	6.0	8.8	5.6	7.4	0.4	1.6	5.2	16.0
2	36.4	18.8	9.2	4.8	3.4	4.8	2.8	1.2	1.6	17.0
3	20.4	24.0	8.8	8.4	5.4	2.4	4.0	3.2	6.0	17.4
4	24.4	20.4	15.2	8.0	2.0	5.2	2.0	1.2	2.0	19.6
5	32.8	20.0	6.4	4.4	6.8	2.8	2.4	2.0	4.8	17.6
6	31.2	12.8	7.2	7.8	6.4	6.0	6.8	0.8	0.4	20.6
7	27.2	21.6	8.8	3.2	4.4	3.2	2.8	0.8	3.2	24.8
8	34.8	20.8	8.0	4.8	2.0	3.2	4.4	0.8	1.2	20.0
9	44.0	30.4	3.2	3.0	2.0	0.8	2.8	0.8	0.4	12.6
10	20.4	24.0	16.8	7.2	6.5	3.6	2.0	0.8	2.4	16.3
11	13.6	12.0	30.0	12.4	5.2	1.2	2.0	4.4	0.8	18.4
12	19.2	16.4	20.0	10.4	4.4	3.2	1.2	4.0	0.8	20.4
13	21.6	25.2	11.2	8.8	6.4	4.0	2.4	2.0	4.0	14.4
14	44.4	15.2	8.8	8.0	2.0	0.8	3.2	0.4	0.8	16.4
15	24.4	18.0	16.4	8.0	4.8	4.4	3.2	3.2	0.8	16.8

oils do not meet this requirement. They are much less soluble. The Eleventh Revision of the U. S. P. stipulates the solubility of one volume of Oil *Pinus Pumilio* in 4.5 to 8 volumes of 90% alcohol. Generally this does not conform to pure oils since in many cases a clear solution is not obtained.

According to the U. S. P. X and XI Oil *Pinus Pumilio* has an ester content of not less than 5% calculated as Bornyl Acetate. As a matter of fact, however, genuine oils are often below this limit.

As to optical rotation, the U. S. P. X specifies −4° 30′ to −9° in 100-mm. tube at 25° C. These figures are incorrect according to our investigation because genuine Tyrolean oils have an optical rotation from −3° 19′ to −15° 16′. Therefore it is to be regretted that the Eleventh Revision of the U. S. P. requires a rotation of −5° to −12°.

Regarding boiling range, the U. S. P. X states that less than 1% of the oil distils below 165° C. Similarly, Gildemeister and Hoffmann (5) and later the annual reports of Schimmel and Co. allow for only 1% to distil below 165° C. if the oil is to pass as pure. None of these twenty-four authentic oils met this requirement although many of our shipments received during past years have conformed to this requirement. However, these samples conform with the U. S. P. XI, which specifies that less than 10% of the oil distils below 164° C., in the case of all oils examined, except Sample 15. Climatic conditions and other circumstances seem to

Table VII.—Limits of Gildemeister and Hoffmann, the U. S. P. X and the U. S. P. XI for Oil *Pinus Pumilio*

	Gildemeister and Hoffmann	U. S. P. X	U. S. P. XI
Specific gravity	0.860 to 0.875 at 15° C. (0.854 to 0.869 at 25° C.)	0.853 to 0.869 at 25° C.	0.853 to 0.869 at 25° C.
Optical rotation	−4° to −15° 20′	−4° 30′ to −9°	−5° to −12°
Refractive index at 20° C.	1.475 to 1.480	1.4750 to 1.4800	1.4750 to 1.4800
Acid value	Up to 1.0	.....	.....
Ester content (calculated as Bornyl Acetate)	3 to 8%	Not less than 5%	Not less than 5%
Solubility	4.5 to 8 volumes of 90% alcohol, sometimes with turbidity	10 Volumes of 80% alcohol	4.5 to 8 volumes of 90% alcohol
Boiling range:			
Up to +165° C.	Nothing	Less than 1%	Less than 10%
+165° C. to +170° C.	Up to 15%	.....	.....
+170° C. to +175° C.	14 to 40%	.....	.....
+175° C. to +180° C.	12 to 40%	.....	.....
+180° C. to +185° C.	8 to 12%	.....	.....
Above +185° C.	24 to 36%	.....	.....

have a great influence on the properties of Oil *Pinus Pumilio* especially on the boiling range.

In this connection it might prove of interest to list the known constituents of Oil *Pinus Pumilio*.

Known Constituents of Oil Pinus Pumilio:

l-α-Pinene (6)
β-Pinene (7)
l-Limonene (8)
Dipentene (9)
Δ^3-Carene (10)
l-Phellandrene (11)
An aldehyde, $C_{15}H_{26}O$ (12)
A ketone, $C_{15}H_{24}O$ (13)
Caproic aldehyde (14)
Sylvestrene (15)
Cuminic aldehyde (16)
Anisic aldehyde (17)
Δ^3-Isopropyl-4-cyclohexenone (18)
A secondary, unsaturated, monocyclic terpene alcohol, $C_{10}H_{18}O$ (19)
An unsaturated sesquiterpene alcohol, (Pumiliol), $C_{15}H_{26}O$ (20)
Bornyl acetate (21)
Bornyl propionate (22)
Bornyl capronate (23)
A sesquiterpene (cadinene?) (24)
Unidentified tertiary terpene and sesquiterpene alcohols (25)

As can be seen from the above listed constituents, there are present several low boiling terpenes, α-Pinene (boiling point 154° C.), β-Pinene (boiling point 164° C.).

A possible explanation for the apparent change (from the reported literature) in the boiling range is the presence of relatively larger amounts of α- and β-Pinene which in turn might be due to a great number of circumstances; for example, changes in the condition of soil, climate, harvesting, gathering, time of distillation, distillation material (twigs, needles, bark, etc.) and age of tree.

Table VIII.—Limits of Shipments of Tyrolean Oil *Pinus Pumilio*

Specific gravity at 25° C./25° C.	0.857 to 0.864
Optical rotation	−7° to −13°
Refractive Index at 20° C.	1.4750 to 1.4770
Ester content (calculated as Bornyl Acetate)	3.3 to 5.9%
Solubility at 25° C.	Soluble in 5 volumes and more of 90% alcohol; to turbid in 10 volumes of 90% alcohol
Boiling range	Up to 2.8% distils below +165° C.

Oil of *Abies Alba*. The limits of Gildemeister and Hoffmann, "Die Ätherischen Öle" (26) which are generally accepted as standards, are given for Oil *Abies Alba* in Table IX.

Table IX.—Limits of Gildemeister and Hoffmann for Oil *Abies Alba*

Specific gravity at 15° C.	0.867 to 0.886
Optical rotation	−34° to −64°
Refractive index at 20° C.	1.473 to 1.476
Ester (calculated as Bornyl Acetate)	4.5 to 11%
Solubility	Soluble in 4 to 7 volumes of 90% alcohol, sometimes with slight turbidity
Acid Value	Up to 2.0
Boiling Range:	
Below +170° C.	8%
+170° C. to +185° C.	55%

In the following discussion Samples 9 and 14 are excluded, since these two oils were distilled exclusively from bark.

Samples 2, 6, 12 and 15 failed to comply with the requirement of Gildemeister and Hoffmann for

optical rotation; Sample 15, the requirement for solubility; samples 2, 6, 10, 11, 12 and 13, the requirement for ester content; all samples, the requirement for boiling range. However, all these samples met the requirements for refractive index, specific gravity and acid value. Of these thirteen oils, none met all the requirements set forth by Gildemeister and Hoffmann.

As a matter of interest the analyses of shipments of Tyrolean Oil *Abies Alba* received in the last few years are presented in Table X (27).

Table X.—Limits of Shipments of Tyrolean Oil *Abies Alba*

Specific gravity at 15° C. /15° C.	0.873 to 0.876
Optical rotation	−41° to −47°
Refractive index at 20° C.	1.4729 to 1.4749
Ester content (calculated as Bornyl Acetate)	5.2 to 8.5%
Solubility at 20° C.	Soluble in 5 to 10 volumes and more of 90% alcohol
Boiling range.	Up to 41% distils below +165° C. Up to 22% distils between +165° C. to +170° C.

According to our investigation, the boiling ranges obtained for Oil *Abies Alba* differ considerably from the limits reported in the literature. Whereas in the past years Oil *Abies Alba* might have had a boiling range such as indicated in Gildemeister and Hoffmann, oils distilled in recent years give upon distillation a fraction below +170° C. of about 55% and even more. As in the case of Oil *Pinus Pumilio* the same factors may be responsible for this change, since a listing of the known chemical constituents of Oil *Abies Alba* shows the presence of α-Pinene.

Known Chemical Constituents of Oil Abies Alba:

l-α-Pinene (28)
l-Limonene (29)
l-Bornyl acetate (30)
A sesquiterpene (31)
Lauric aldehyde (32)
Decylic aldehyde (33)
Santene (34)

SUMMARY

This investigation of Oil *Pinus Pumilio* and Oil *Abies Alba* has shown that the limits for physico-chemical properties as set forth in the literature are not altogether in agreement with our findings for genuine Tyrolean oils. Therefore, these limits should be revised. On the basis of genuine oils of commerce, these samples of unquestionable purity and the literature, we recommend the following limits for Tyrolean oils:

Oil of *Pinus Pumilio*

Specific gravity at 25° C. /25° C.	0.853 to 0.871
Optical rotation	−3° to −16°
Refractive index at 20° C.	1.4750 to 1.4800
Ester content (calculated as Bornyl Acetate)	3 to 10%
Solubility at 25° C.	Soluble in 4.5 to 10 volumes of 90% alcohol, often with turbidity
Boiling range	Less than 10% distils below +165° C.

Oil of *Abies Alba*

Specific gravity at 15° C./15° C.	0.867 to 0.880
Optical rotation	−13° to −67°
Refractive index at 20° C.	1.4729 to 1.4760
Ester content (calculated as Bornyl Acetate	Up to 11%
Solubility at 20° C.	Soluble in 4 to 10 volumes of 90% alcohol, sometimes with slight turbidity
Boiling range	Since as much as 55% and more distils below +170° C., any definite recommendation would be meaningless

REFERENCES

(1) Gildemeister, E., and Hoffmann, F., "Die Ätherischen Öle," 3rd Edition.

(2) Guenther, E., "Tyrolean Oils," *Am. Perfumer*, 31 [6] (1936), 54; 32 [1], (1936) 62; 32 [2], 60; 32 [3], 56.

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Some of the Constituents of the Tuber of "Coquí" (*Cyperus Rotundus L.*)

I. Preliminary Examination of the Tuber and Composition of the Fatty Oil

*By Conrado F. Asenjo**

"Coquí" is the common name given in Puerto Rico to a sedge, perennial by long tuber-bearing rootstocks. It is known in English-speaking countries under the name of nut grass. This sedge is not restricted to this particular tropical area but, on the contrary, it is widely distributed all over the tropical and sub-tropical belts. Often it becomes a pernicious weed (1). Botanically, the plant has been identified as *Cyperus rotundus* L., family Cyperacea (1). The only other plant of this genus to have been phytochemically studied to any extent is *Cyperus esculentus* L. (2).

The tubers of "coquí" are easily available in the fruit markets of Puerto Rico. Our supply came from San Juan, Puerto Rico. When fresh, these tubers have an aromatic odor and possess a bitter-cool taste. In color they are dark brown on the outside and whitish or yellowish within. They have an ovoid shape, measuring from 0.5 to 1.5 cm. in diameter. Each tuber weighs, when fresh, from 1 to 3 Gm.

A water infusion, prepared by boiling the whole tuber, has been used in Puerto Rico for a long time in the treatment of kidney and urinary disorders. It is the common belief that this infusion stimulates diuresis and dissolves urinary stones.

Although the drug is known from very old (3)—the *Kupeiros* of the Greeks—and has been, in the past, official in several pharmacopœias,[1] the literature does not reveal any chemical or pharmacological investigations, either of the tuber[2] or of any other part of the plant. A gross pharmacognostical examination of this tuber has been made by Goebel-Kunze (5).

The present investigation deals with the air-dried drug and consists of an attempt to elucidate the chemical composition of this tuber.

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[1] The Pharmacopœias, in which *C. rotundus* L. tuber is official, are:

Country	Edition	Date
Danish	1	1772
French	1	1818
Mexican	1	1874
"	2	1884
"	3	1896
"	4	1904

It is also recorded in the Chinese Pentsaos, according to Stuart (4), under the name of Hsiang-fu-tzu.

[2] The volatile oil from the tuber has been examined by several investigators. We shall deal with it in a future publication.

EXPERIMENTAL

Table I.—Proximate Analysis of "Coquí" Tuber (Average of Three Determinations)

Constituent	Per Cent Wet Basis	Per Cent Dry Basis
Moisture	48.73	...
Nitrogen free extract	42.06	82.10
Protein (N × 6.25)	1.87	3.63
Ether extractive	1.20	2.31
Crude fiber	4.04	7.86
Ash	2.10	4.10

Extraction with Selective Solvents.—The tubers were dried at 80° C. in a circulating air oven for about 24 hours. Then they were comminuted in a Wiley mill to particles about 10 mesh. The moisture content of this material averaged 9.4 per cent and the ash content, 3.56 per cent. Triplicate determinations were performed in percolators, using continuous extraction. The petroleum ether extractive averaged 2.3 per cent, the ether extractive, 0.8 per cent, and the alcoholic extractive, 17.7 per cent. The mark left, after extracting with the above solvents, was subjected to extraction with boiling water, but a mucilaginous mass resulted.

The Fatty Oil.—After subjecting the petroleum ether extractive to steam distillation to get rid of the volatile oil, the non-volatile fraction left in the flask was recovered with ether.[1] The oily substance remaining, after evaporating the ether, had a specific gravity of more than one, and amounted to 82.5 per cent of the petroleum ether extractive. When shaken with petroleum ether, only part of this oil went into solution, leaving behind a resinous brown mass. After evaporating the petroleum ether, a lighter oil was obtained which had the following constants (6): sp. gr. at 20° C.—0.9500; ref. ind. at 20° C.—1.4967; iodine no. (Hanus)—87.95; sap. no.—134.30; acetyl no.—63.30; unsap. %—22.80; acid no.—35.20.

Waxy Neutral Substance.—After saponifying the oil and neutralizing the mixture with acetic acid, a waxy substance separated, which would not dissolve either in acid or alkaline solutions. This substance was easily purified by dissolving it in hot alcohol and recovering from the cold solvent. To remove the last traces of color, it was shaken with hot dilute HNO_3 and then refluxed with acetone. On cooling the acetone, a white, amorphous, waxy precipitate separated, which melted sharply at 97–98° C. and burned with a smoky flame, leaving no ash. It amounted to about 2.7 per cent of the oil.

Unsaturated Acids.—The unsaturated acids were separated by the lead salt-ether method (7). Identification of the unsaturated acids was effected by means of their bromo addition compounds and their separation by the use, in turn, of ether and petroleum ether. The precipitate obtained from the ethereal solution, m. p. 182° C., after being recrystallized from ether, indicates the presence of linolenic acid (hexabromide of linolenic acid, m. p. 182° C.). The petroleum ether solution yielded, after standing in the ice-box, a precipitate which melted after recrystallization at 114° C., indicating the presence of linolic acid (tetrabromide of linolic acid, m. p. 114° C.). The residual fraction was debrominated by refluxing the alcoholic solution with zinc dust. The zinc oleate formed was decomposed with sulfuric acid into oleic acid and zinc sulfate. A drop of the oleic acid recovered was dissolved in a few cc. of concentrated sulfuric acid. On superimposing a diluted alcoholic solution of vanillin, a violet-colored ring appeared at the interface of the two solutions. This is a specific color test for oleic acid. The remainder of the oleic acid was oxidized with 10 per cent alkaline potassium permanganate. A white crystalline precipitate was obtained which melted after several recrystallizations from alcohol at 130° C. (dihydroxystearic acid, m. p. 131.5° C.).

Saturated Acids.—A separation of the saturated acids was performed by taking advantage of the selective solubility of the lead salts in boiling ethyl alcohol. The insoluble part of the lead salts was separated by filtration. The sparingly soluble lead salts yielded an acid, m. p. 66–70° C., after several recrystallizations. This acid has a waxy consistency and is probably stearic acid, m. p. 69.3° C. Because of the small amount obtained, no further attempts were made to characterize it. The soluble lead salt yielded an acid with a melting point of 53–54° C. after recrystallization. This melting point agrees with that of myristic acid, m. p. 53.8° C.

Glycerol.—The aqueous solution left after the liberation of the fatty acids was evaporated, as far as possible, on the steam bath. A few drops of this syrup gave, when heated with potassium bisulfate, a faint odor of acrolein.

Unsaponifiable Matter.—A preliminary examination of the unsaponifiable matter shows that it contains 5.5 per cent sterols when estimated by the digitonide procedure. On acetylation, a small amount of crystals, melting at 125–128° C., was obtained (α_2 sitosterol acetate, m. p. 124–126° C.).

[1] The water left, after shaking out the ether-soluble part, gave a strong Fehling's test for reducing sugars. This suggests the presence of a glycoside in the original petroleum ether extractive. This glycoside is probably broken up into its sugar and aglucone during the process of steam distillation.

SUMMARY

1. The history, distribution, botanical classification and folk uses of the tuber of *Cyperus rotundus* L. are given.

2. The proximate analysis of the tuber is reported; also the yield of extractives when treated with selective solvents.

3. The principal constants of the fatty oil were determined. This oil contains, besides a large amount of unsaponifiable

matter, a neutral waxy substance, m. p. 97–98° C.; glycerol; linolenic; linolic; oleic; myristic and, possibly, stearic acid.

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Notes on Mexican Drugs—I. Zapote borracho (*Lucuma salicifolia* Kunth, Sapotac.)

*By Marcel Bachstez and Allagracia Aragon**

In his book, "Magische Gifte," V. A. Reko (1) describes the intoxicating effects of a peculiar Mexican fruit. This fruit, "Zapote borracho" ("drunk zapote"), is when unripe yellowish green, when ripe dull orange-yellow with yolk-yellow pulp. It can be bought in the markets of Oaxaca, Tehuacan, Puebla, and at times in Mexico City.

As the fruit is frequently eaten and no investigation appears to have been made of its constituents, it was decided to undertake such an investigation to determine if it contains any active principles.

"Zapote borracho" is identified as *Lucuma salicifolia* Kunth. The literature on the plant is very limited and is mainly devoted to the botanical aspect. Wilson Popenoe devotes in his "Manual of Tropical and Subtropical Fruits" (2) only a few lines to the fruit. He points out its similarity to the "canistel," which grows in the Florida Keys and in Cuba, but he does not give any information on its composition or its physiological action.

From our investigations, it can be stated that neither glycosides nor alkaloids are present. Extensive inquiries have also convinced us that this frequently eaten fruit has no harmful properties. It is probable that the popular Mexican name for the fruit, "Zapote borracho" ("drunk zapote"), has reference to the musty, alcoholic smell

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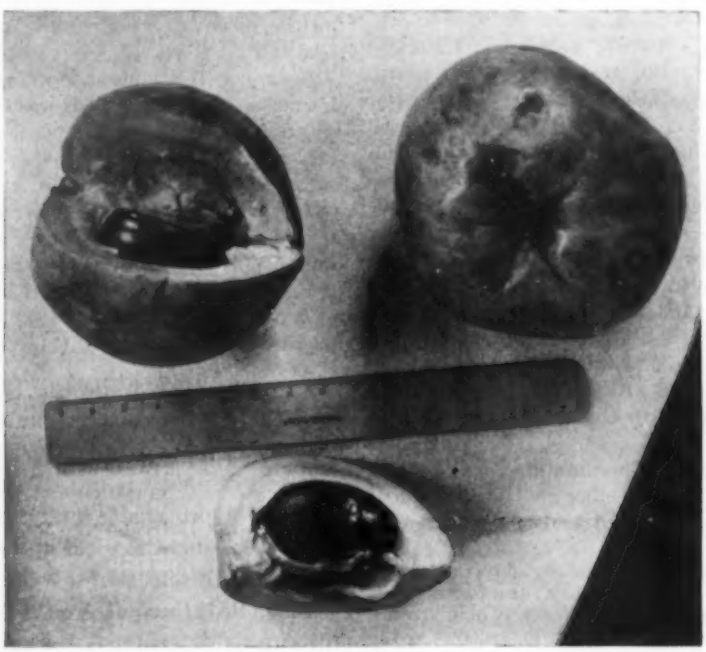

Fig. 1.

of the fruit, when overripe, and not to any intoxicating effect.

EXPERIMENTAL

The water content of the fruit, determined by the method of the A. O. A. C. (3) was found to be 66.13%, total ash 0.52%. The alkalinity of the fruit (referred to 100 Gm.) was found to be 16.6. The ash is rich in iron.

Preliminary Examination.—A hot water infusion gave a filtrate acid to litmus, p_H 4.0. The infusion gave with ferric chloride tests for tannins. Very little foaming was observed on shaking, indicating the absence or the presence of only minute quantities of saponins. Iodine showed the presence of starch. Steam distillation did not indicate volatile constituents. Dilution of portions of the filtered decoction remaining from the steam distillation with alcohol produced a gummy precipitate indicative of mucilage or pectin (4); but the amount of precipitate was very small.

Alkaloids, Glycosides and Carbohydrates.—Extraction of the fruit with Prollius' fluid and with weak hydrochloric acid at different temperatures gave negative results with the usual alkaloidal reagents. The method of Stas-Otto (5) gave no indication of glycosides or of alkaloids. Carbohydrates are present.

Protein.—The fruit contained 14.5% of protein as determined by the Kjeldahl method (6).

General Method.—The fruit (50 Gm.) was extracted in a Soxhlet extractor with selective solvents (7) and the following results were obtained:

(*a*) Petroleum ether: Minute quantity of dark colored resin, 2%.

(*b*) Ether: Minute quantity of resin.

(*c*) Chloroform: Resin, 1%.

(*d*) Alcohol: Yellow coloring matter, minute quantities of tannin and carbohydrates.

(*e*) Insoluble in water (8): 12% of the fruit material.

The alcoholic extract was taken up with water and gave the following reactions for carbohydrates: Barfoed's reaction (9), positive, indicating monosaccharides; Bial reaction (10), negative, showing the absence of pentoses; Seliwanoff's reaction (11), positive, showing the presence of fructose. The presence of sucrose was demonstrated by Rothenfusser's method (12).

The percentage of carbohydrates naturally varies with the ripening of the fruit. By the methods of the A. O. A. C. (13) there were found 14.85% of sucrose and some invert sugar at one stage and 2.7% of sucrose and 12.2% of invert sugar at maturity. This accords with the glucose percentage, 10.3%, as determined by the method of Willstaetter and Schudel (14).

SUMMARY

"Zapote borracho" contains tannin, starch, protein (14.5%), carbohydrates (14.85%) and water (66.13%), but no glycosides or alkaloids. It would appear, therefore, that the fruit is quite harmless and that it possesses no intoxicating properties.

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Advantages of Iso-Alcoholic Elixirs of National Formulary VI*

By J. W. Millar, S. J. Dean and R. A. Marshall

A partial survey of the retail pharmacies of this area (San Francisco and vicinity) has shown that many pharmacists are not taking advantage of the Iso-Alcoholic Elixirs, with the result that in most cases the Elixirs of the National Formulary are purchased in one pint or larger quantities and may remain upon the shelves of the prescription department for long periods of time, thereby losing much of their potency, due to exposure to light, change of temperature and various other causes, and becoming sufficiently altered so that the physiological action expected from their use is often lacking.

It is therefore proposed that many of these Elixirs be prepared extemporaneously, using the Iso-Alcoholic Elixirs so as to obtain the desired alcoholic content in the finished product—it being necessary then to add only the medicinal constituents to the predetermined iso-alcoholic mixture. The ad-

* A contribution from the laboratories of the College of Pharmacy, University of California, Medical Center, San Francisco, California.

Table I.—Alcoholic Content of Elixirs

Elixir	Low Elixir	High Elixir	% Alcohol N. F. Monograph	% Alcohol in Extemperaneous Preparations
1. Almond Comp.	1	(1 Water)	3–5	4.2
2. Aminopyrine	6	1	17–20	18.7
3. Arom. Rubrum	4	1	22–24	22.4
4. Barbital	2	1	29–32	31.0
5. Calc. Lacto-phos.	6	1	17–20	18.6
6. I. Q. and S.	4	1	22–24	22.1
7. Pepsin	12	1	13–15	14.1
8. Pepsin Comp.	7	1	16–19	17.3
9. Phenobarb.	6	1	17–20	18.5
10. Rhei. Alk.	3	2	34–38	35.8
11. Sod. Brom.	2	(1 Water)	5–7	5.8
12. Terpin Hyd.	1	1	38–42	42.2
13. Triple Brom.	1	(1 Water)	3–5	4.35
14. Vanilla Comp.	5	(1 Water)	7–9	7.6

vantages of this method are that the Iso-Alcoholic Elixirs of the National Formulary suffer no deterioration over long periods of time and may therefore be prepared in quantities of one gallon or more and used as required for the extemporaneous preparations.

No difficulty has been encountered in this laboratory in the preparation of the various Elixirs of the N. F. by this method and in many cases the time required for preparation has been materially decreased.

A 1 per cent solution of Amaranth was substituted for Cudbear in the Iso-Alcoholic Elixirs of Amino-pyrine, Aromatic Rubrum, Pepsin Compound and Phenobarbital. This substitution has given, we believe, a greater brilliancy and is less affected by light exposure and change of p_H.

It has been observed that in the case of Elixir of Phenobarbital, where the prescribed amount of Phenobarbital is in excess of that required for the Official Elixir of Phenobarbital in the N. F., sufficient of the high Iso-Alcoholic Elixir should be used to obtain at least a 30 per cent alcoholic vehicle, this being in accord with the findings of Fantus and Dyniewicz (1, 2).

EXPERIMENTAL

Fourteen elixirs were prepared according to the directions of the National Formulary VI, also fourteen duplicates were prepared using the Iso-Alcoholic Elixirs of the N. F.

The alcoholic content was determined in the samples prepared from the iso-alcoholic elixirs.

Each pair of samples of the duplicate sets of Elixirs was compared as to color, odor and taste and found to be identical. After standing over a period of more than ninety days, no apparent change had occurred.

SUMMARY

(1) The use of the Iso-alcoholic Elixirs of the N. F. permits the pharmacist to prepare the elixirs of the N. F. extemporaneously at a considerable saving of time.

(2) The extemporaneous preparations are strictly comparable with the same elixir of the N. F. as to alcoholic content, color and taste.

(3) Amaranth may be substituted for Cudbear to advantage in some elixirs.

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Particle Size Studies

II. The Grain Size Distribution of Bismuth Subsalicylate U. S. P.*

By John J. Corcoran† and Sister Mary Etheldreda, F.S.S.J.‡

INTRODUCTION

The Pharmacopœia (1) describes Bismuth Subsalicylate as "an amorphous or microcrystalline powder." New and Non-Official Remedies (2) lists as accepted one brand of the drug and ten oil-suspensions of the product. Since for the best development of the action of the drug as well as for its mechanical suspension in oil, a very fine divi-

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Table I.—Grain Size Distribution of Particles as Percentage by Weight Finer than Size in Six Samples of Bismuth Subsalicylate, U. S. P. XI

T (Min.)	H (Cm.)	Grain Size (Microns)	Percentage by Weight Finer than Size					
			Mfg. A	Mfg. B	Mfg. C	Mfg. D	Mfg. E (Reg.)	Mfg. E (Spec.)
5	19.7	18.68	78.6	87.8	87.4	83.2	86.4	98.6
15	19.4	10.70	69.4	87.4	84.4	82.6	79.8	98.0
30	19.0	7.48	55.4	77.2	74.8	76.8	12.6	96.0
60	18.7	5.24	54.0	50.6	62.8	63.4	7.0	95.6
120	18.4	3.68	27.6	30.4	52.2	39.2	3.8	92.8
240	18.0	2.57	20.2	18.6	39.4	17.4	3.0	90.4
360	17.7	2.08	15.6	14.6	31.8	11.2	2.6	90.0
1440	17.4	1.02	6.4	4.0	18.2	2.2	1.4	76.2

Table II.—Grain Size of Particles as Percentages by Weight in Distribution Intervals in Six Samples of Bismuth Subsalicylate, U. S. P. XI

Mfg.	$<-1.02\ \mu$	1.02–2.57 μ	2.57–7.48 μ	7.48–18.68 μ	>18.68
A	6.4	13.8	35.2	23.2	21.4
B	4.0	14.6	58.6	10.6	12.2
C	18.2	21.2	35.4	12.6	12.6
D	2.2	15.2	59.4	6.4	16.8
E (Reg.)	1.4	1.6	9.6	73.8	13.6
E (Spec.)	76.2	14.2	5.6	2.6	1.4

sion of the salt is essential, we have determined the grain size distribution in six commercial samples of this drug.

EXPERIMENTAL

The test was conducted by the method described by the authors in a previous communication to this JOURNAL (3). The grain size was calculated from Stoke's law according to the falling velocities of the particles (h/t). When the test is conducted at 25° C. on material with a specific gravity of 3.0 and distilled water used as the suspending medium,

$$r \text{ is equal to } 5.84\sqrt{H/T} \qquad (1)$$

with r, the radius of a spherical particle, in microns; H in cm. and T in minutes. Applying Stoke's law to cubes, the width of a cube is equal to 1.612 r. Thus, the grain size of the particles, calculated as cubes is

$$\text{Grain size is equal to } 9.414\sqrt{H/T} \qquad (2)$$

The results are tabulated in Tables I and II.

SUMMARY

1. The grain size distribution in six samples of Bismuth Subsalicylate, U. S. P. XI has been determined.

2. In five of the six samples tested, 80 per cent of the particles have a grain size less than 20 microns. In one sample (labeled "special" by the manufacturer), 90 per cent of the particles have a grain size less than 3 microns.

CONCLUSIONS

The Pharmacopœia might properly describe Bismuth Subsalicylate as an amorphous or microcrystalline powder in which not less than 80 per cent of the particles have a grain size smaller than 20 microns.

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The Vitamin B Complex*

(A Review)

By Douglas Frost†

INTRODUCTION

Few subjects could offer more lively interest or greater intricacy of thought than that of the vitamin B-complex. What it is, where it is found, how it functions, how its presence can be detected and quantitatively assessed, and how it can best be used, are questions of fundamental importance in biology and medicine. Indeed, they are tantamount to our understanding of many of the innermost secrets of cellular life.

Although the idea of the vitamin B complex was born in the minds of a few far-seeing men several decades ago, it remained quite vague and intangible in the popular mind until only recently. Now we are on very firm ground in discussing the B com-

* An address to the AMERICAN PHARMACEUTICAL ASSOCIATION, Chicago, Illinois, December 1940.

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plex, and particularly those five crystalline, synthetic B-complex vitamins which intensive research has made available to us in a few short years. Thiamin (vitamin B_1), riboflavin (part of vitamin B_2), nicotinic acid (part of vitamin B_2), pyridoxine (vitamin B_6—identical with B_5) and pantothenic acid (identical with B_3) are all well-characterized chemical compounds and are now being synthesized on a large scale. There is no more mystery about those compounds from an organic chemist's point of view than there is about aniline, phenolphthalein or the amino acids.

BIOLOGICAL SIGNIFICANCE

From the biochemist's point of view, certain facts about the above five compounds appear to stand out and to make understandable their role in life processes. These facts serve to establish the importance of the vitamin B complex generally and to show how logical its place in biological science has become.

1. All five B-complex vitamins occur in relatively high amount in actively metabolizing tissue, such as liver and kidney. They also occur in high amount in yeast and bacteria, and also in seeds and sprouts of all plants.

2. Each of the five is known to function as the active grouping of an enzyme system intimately concerned with intermediary metabolism, and is known to affect the rate of metabolism adversely in its deficiency. Probably each one is essential to the metabolic integrity of all living things.

3. Although differing widely in chemical nature, each of these compounds, as it occurs naturally, is water-soluble and is capable of forming soluble protein complexes.

4. All of them have been shown to stimulate the growth of rats, chickens and dogs when given in extremely small amounts. All of them have been shown to stimulate growth in certain species of plants and microorganisms. Thus they can be regarded as the organic catalysts of metabolism, which may or may not be required in the nutrition, depending on the species in question.

HISTORY

The story of the vitamin B complex has unfolded rapidly in the last six years. Each year has seen the isolation, characterization or synthesis of one of the above-mentioned generally recognized B-complex vitamins. To recount the immense number of experiments and observations which led to the eventual isolation, characterization and synthesis of any one of them would require several volumes. A number of books (1, 2, 3) have already appeared to tell the story of vitamin B_1. Reviews on riboflavin (4, 5), nicotinic acid (5), vitamin B_6 and pantothehic acid have also appeared. In this brief review I cannot begin to do justice to these stories. Suffice it to say that the isolation of each of the five compounds as biologically important substances followed somewhat the same pattern. Thus, the heat-stable factor in yeast, liver, eggs and milk, which has so much to do with the growth-promoting value of these foods, turned out to be riboflavin, the same beautiful yellow pigment of milk serum, the occurrence of which was reported in 1784 (6). Simultaneously with the announcement of its isolation as a growth factor for rats in 1932 (7) came the news that this same yellow pigment is the prosthetic group of an enzyme which occurs in yeast and has a great deal to do with the mechanism of fermentation (8). In rapid order, riboflavin was isolated from milk, eggs, liver, kidney, urine and barley. Because it was a new compound, unknown to organic chemists, it had to be characterized. When the nature of the compound was determined, the generic name "flavin" was applied to it and to similar type compounds which might be subsequently isolated or synthesized in the laboratory. As it turned out, *d*-riboflavin is the only naturally occurring flavin, although a great number of other flavins have been made. As might be expected, Nature made no mistake in making riboflavin as it did, for, of all the flavins, riboflavin is most active in all species, whether in plants or in animals.

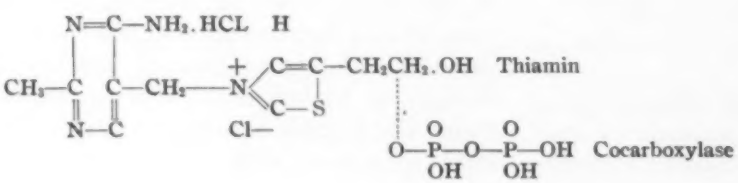
The substance in liver extracts which had most to do with the cure of black-tongue in

dogs and which, according to Goldberger, might be expected to cure the analogous disease, pellagra, in humans, turned out to be nicotinic acid (9). Nicotinic acid had been made from nicotine in 1867 (10) and had been isolated by Funk in 1912 (11) in his search for vitamin B_1. In fact, nicotinic acid had followed Funk's fractions so closely that he had patented the procedure for isolation of crystals which were undoubtedly nicotinic acid, but which carried sufficient vitamin B_1 as an impurity to be a relatively rich source of that vitamin. The fundamental discovery of Warburg (12) that nicotinamide is the functional grouping of an important respiration enzyme found in blood cells provided the clue (13) which led directly to recognition (9) of the nutritional importance of nicotinic acid and its derivatives.

Vitamin B_6 was isolated from rice bran concentrates (14) as the curative factor for a typical dermatitis in rats called acrodynia. When the pure compound became available it was found to do many surprising things. It promptly cured a certain type of microcytic anemia in dogs (15) and pigs. It promoted the growth of chicks (16) and microorganisms (17) and it has been reported to relieve muscle dystrophy in humans (18).

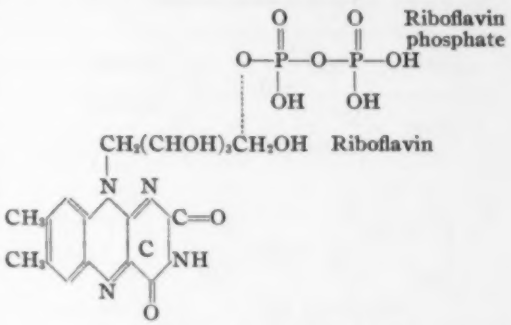
Pantothenic acid (19) was first recognized about 20 years ago as a growth factor for yeast. Its final characterization (20) was made possible as a specific growth factor for yeast and for lactic acid-producing bacteria and as the chick antidermatitis vitamin. Although synthesis of pantothenic acid was announced only eight months ago, it is already known to be required by chicks (21), rats (22) and dogs (23), and there is some evidence that it plays a role in human nutrition (24) as well.

Chemistry and Stability of the B-Complex Factors.—Thiamin hydrochloride has the structure:



This is the form in which synthetic thiamin is dispensed generally. About 80–90% of naturally occurring thiamin is found as the pyrophosphoric acid ester, cocarboxylase. Unfortunately, thiamin is not as stable as cocarboxylase under certain conditions and requires special handling. Both thiamin and cocarboxylase are destroyed by heat and alkali. Thiamin is destroyed also by even mild reducing agents. Stabilization of thiamin can be accomplished in many pharmaceutical preparations, but the job is not so easy as it may seem.

The first heat-stable B-complex vitamin to be recognized as such was riboflavin.



In the free form it is only sparingly soluble in water (0.025%). In its natural form it exists as the pyrophosphate and in combination with adenylic acid and various proteins (*d*-amino acid oxidase, diaphorase, flavin-adenine-dinucleotide).

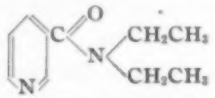
Riboflavin is stable to heat and to strong acids. It is destroyed by alkali and by light. Destruction by light is extremely rapid at alkaline p_H and is appreciable at acid p_H. Both riboflavin and thiamin are quite stable to atmospheric oxygen and to hydrogen peroxide.

Riboflavin is reversibly oxidized to colorless leucoflavin by the proper reducing agents, such as bisulfite, and is rapidly oxidized back to the original yellow compound by merely shaking in presence of oxygen.

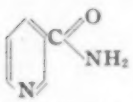
It is this property of easy reversible reduction and oxidation which explains the role of riboflavin in biological oxidations.

The formula of nicotinic acid is quite simple.

Many analogues are active, including:

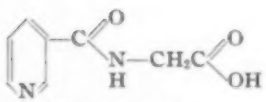


Nikethamide (Coramine)
(Diethyl nicotinamide)

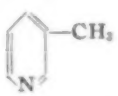


Nicotinamide

Quinolinic acid

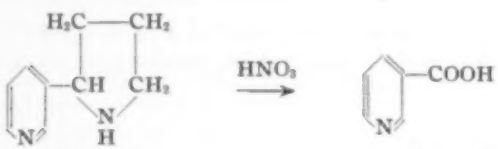


Nicotinuric acid
(Nicotinyl glycine)



B-Picoline

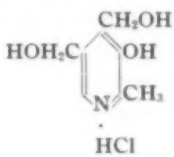
In fact, any compound which yields β-carboxy or β-amido pyridine when taken into the body might be expected to have some anti-pellagric action. Even nicotine, which is the chief source of the manufacture of nicotinic acid chemically, may yield traces of nicotinic acid in the body. It is odd that nicotine, a compound second to hydrocyanic acid in the swiftness with which it will cause death of animals, is so closely related to compounds essential to all life. It also provokes tribute to the long-continued research, much of it into fields of pure knowledge, which makes such a useful transition possible.



Nicotine — Nicotinic acid

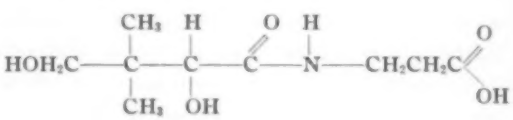
From a chemical and pharmaceutical standpoint, nicotinic acid presents the least difficulties of any of the B-complex vitamins. Nicotinic acid is one of the most stable compounds known to organic chemistry, and nicotinamide is quite stable to ordinary pharmaceutical handling. From a pharmacologic standpoint, nicotinamide is the compound of choice because it is less apt to give the unpleasant secondary flushing and tingling sensations experienced with even small doses of nicotinic acid. Also nicotinamide is much more water-soluble than nicotinic acid, which is usually dispensed as the soluble sodium or ethanolamine salts.

Pyridoxine, formerly known as vitamin B_6 adermin, factor *I*, and factor *Y*, is also a substituted pyridine.



It is quite water-soluble and quite stable to heat, oxidation and acid. It is less stable to alkali and is quite rapidly destroyed by alkaline oxidation. Pyridoxine is amphoteric but, unlike nicotinic acid, it is a stronger base than an acid and is quite generally dispensed in the form of its hydrochloric acid salt. Pyridoxine contains a phenolic hydroxyl grouping and undergoes many type reactions of the phenols, some of which are useful analytically and will be discussed later.

The most recently synthesized member of the vitamin-B complex is pantothenic acid:



It is formed by the interaction of α,γ-dihydroxy-β,β-dimethyl butyric acid with β-alanine. It is destroyed by dry heating or by acid or alkaline hydrolysis and is handled safely only as its neutral salts. Pantothenic acid is dispensed pharmaceutically as the nicely powdered calcium salt. A concentrated water solution of this has a p_H about 8. The p_H of greatest stability is thought to be between 5 and 6. Pantothenic acid is stable to oxidation in air and is stable to ordinary light.

Table I

	Heat	Acid	Alkali	Oxidation	Light
Thiamin	+	++	−	−	++
Riboflavin	++	+++	−	+++	−
Nicotinic acid	+++	+++	+++	+++	+++
Pyridoxine	++	++	−	−	++
Pa A	−	−	−	++	++

+++ = stable, ++ = very slowly destroyed, + = slowly destroyed, − = rapidly destroyed.

Table I indicates the relative stability of the five synthetic B-complex vitamins in aqueous solution under various conditions. Although such a table is of general value, it should be realized that many conditions other than those indicated may contribute to the instability of these compounds and much experimentation must be done before positive assurance of their stability in any preparation can be had. Also the time of reaction is important and a preparation which may appear stable for a week may show a significant decline in potency in a month. Temperature, p_H, oxidation-reduction potential and the nature of the solvent are factors in the stability of all, excepting only nicotinic acid, which is remarkably stable under most conditions.

ANALYSIS

There are rapid chemical or microbiological methods of analysis available now for each of the five mentioned compounds. In some cases these methods are actual improvements from the standpoint of accuracy over the animal assay methods.

Wide use is being made of the thiochrome method of analysis for thiamin (25). In this method cocarboxylase can be converted to free thiamin by hydrolysis in acid. The total thiamin is then oxidized to the blue fluorescent thiochrome by ferricyanide and the thiochrome quantitatively measured in a photoelectric fluorometer. The method is both rapid and accurate and can replace the animal assay in routine testing of many materials.

Vitamin B_6 reacts with such well-known phenol reagents as diazotized sulfanilic acid, the Folin-Denis reagent, and 2,6-dichloroquinone chlorimide. The last reagent produces a blue color soluble in butyl alcohol, which can be measured quantitatively in the photoelectric colorimeter (26). Animal assay methods may be relied upon to check the accuracy of this method. Both cure of acrodynia and growth increment are useful as an index to B_6 potency of materials.

The reaction of nicotinamide and nicotinic acid with cyanogen bromide and an aromatic amine has been extensively studied for its analytical value. The method has been adapted to photoelectric colorimetry (27) and is quite dependable for routine assay of many materials. Cure of blacktongue in dogs is used wherever necessary, but the method is long, cumbersome and of questionable accuracy.

Microbiological assay methods have great promise for routine testing. The assay of riboflavin and pantothenic acid may be accomplished by use of the same organism, *lactobacillus casei*, with only slight variation in technique (28, 29). In this method media are prepared free of either riboflavin or pantothenic acid, whichever is to be analyzed for. The growth and amount of lactic acid produced by *lactobacillus casei* on these media under the proper conditions are an exact measure of the amount of flavin or pantothenic acid added. The method is sensitive to 0.05 microgram of either compound and is accurate to ±10%.

PHARMACOLOGY

All five compounds have had adequate pharmacological testing with animals (30, 31, 32, 33, 34). The margin of safety between the effective dose and the lethal dose was extremely large in all cases. Massive doses (50–100 times the estimated requirement) have been given to humans with no untoward effect.

HUMAN REQUIREMENT

The daily adult human need for these factors is on the order of:

Thiamin	2–3 mg.
Riboflavin	3–4 mg.
Nicotinic acid	15–25 mg.
Pyridoxine	2–3 mg. (estimated)
Pantothenic acid	15–20 mg. (estimated)

The need for pyridoxine and pantothenic acid in human nutrition has only been tentatively established, but there is little doubt that such a need exists. The require-

ments of growing children for all of these factors are probably as great as those of adults, and the requirements of pregnancy and lactation are probably double those of normal. Much research must be done to determine the optimal intake of these factors under all conditions of health and disease. Reviews on this phase of research have recently appeared (35, 36, 37, 38, 39).

NEWER MEMBERS OF THE VITAMIN B COMPLEX

As far as the new members of the B complex go, we can definitely say that the end is not yet. Although rats can be raised to the adult stage on highly synthetic diets with only the five synthetic B-complex vitamins plus choline, there is good evidence that other factors are needed for optimal health. Pyridoxine and pantothenic acid are undoubtedly the two most important growth-promoting substances of the so-called "filtrate factors" fraction obtained from liver, yeast, rice bran and other good B-complex sources. The additional growth-promoting property of the ether-insoluble filtrate fraction from liver has been ascribed to Factor *W* (22, 23).

Present knowledge relates choline to the B complex; however, it appears to be required in higher amount than the other factors and is synthesized to large extent *in vivo* (40, 41).

Inositol and biotin, long known to be required for growth of yeast as members of the "bios" complex, are now recognized as members of the B complex. Biotin has proved to be identical with vitamin H, the anti-egg white injury factor for rats (42), and is essential to normal pelage in chicks (43) and rats (44). Inositol is required for growth and maintenance of normal fur coats in mice (45) and rats (46).

The disclosure that deficiency of the filtrate fraction of the vitamin B complex causes a predilection toward graying of the fur in rats, foxes, dogs and guinea pigs (47) raised the burning question as to what factors are specifically involved. Pantothenic acid appears now to be most intimately concerned with pigmentation in rats (48, 49), but other factors appear to be involved (50, 51, 52). Recently *p*-amino benzoic acid, which had previously been named as a growth factor for microörganisms, was reported (53) to be a growth factor for chicks and a chromotrichia factor for rats. These findings require confirmation before the importance of *p*-amino benzoic nutritionally can be established. Almost nothing is yet known of the relation of diet to graying in humans.

"Anticanitic," a term which means "opposed to graying of hair," has been proposed (54) as offering some advantages over "anti-achromotrichia" for designation of the various "anti-gray hair" factors.

COMPARATIVE NUTRITIONAL REQUIREMENTS OF SPECIES

Generally, it seems that the more complicated the organism, the more complex are its nutritional requirements, and it seems probable that the requirements of man will eventually be found to comprehend the requirements of all species. Also it seems that the more parasitic an organism is, the more uncompromising it is in its demands from its environment. Thus most pathogenic bacteria must obtain many of the B-complex factors from the tissues or blood of their host, while others (the autotrophs) can live on air and a bit of carbon, sulfur or even iron.

Undoubtedly bacterial symbiosis plays a large part in the nutrition of many forms of animal life. Cattle and sheep are good examples of one extreme in nature's plan of synergistic action between living things. Here all or a large share of the animal's B-complex requirements are supplied by synthesis by bacteria in the animal's paunch. The nutritional requirements of ruminants are greatly simplified by this mechanism. The large majority of animals, on the other hand, require most B-complex factors preformed in the diet. Rats, dogs and pigs are the most studied members of this group, which includes the human. In the case of the rat, certain diets have been demonstrated to favor bacterial synthesis of B-complex vitamins more than others, and difficulty in producing acute specific deficiencies is often experienced because of the uncontrolled generation of B-complex factors

in the animal's tract. The chick is probably least helped by bacterial action, and this may be evidenced by its very complex needs for nutritional factors. Biotin, choline, inositol, *p*-amino benzoic acid, glycine, chondroitin, factor *U*, and factor B_c are some of the compounds and hypothetical factors included among the nutritive requirements of the chick. The nutritive requirements of man have not been completely delineated as yet and the job will be a difficult one; however, workers in this ripe field can draw on a wealth of inference derived from work with many animal species.

An increased or decreased ability to synthesize certain B-complex vitamins can be demonstrated in certain bacteria by culturing them through a great many generations in absence or presence of the compounds in question. This sort of biogenetical adaptation to environment can account for some of the variations in the requirements of higher species. Meat is a good source of nicotinic acid, thus naturally carnivorous animals, *i. e.*, all members of the canine and feline families, may be expected to require nicotinic acid preformed in their diets. It is probably safe to predict, then, that lions, jackals and even sharks could be reduced to a pitiful state of inefficiency, just as are dogs, cats and man, by cutting off their supply or utilization of the single factor, nicotinic acid.

Certain processes, wherever they occur in living things, apparently require the intermediation, or catalytic function, of thiamin, riboflavin and nicotinamide. This fundamental action is probably equally true, though less well proved at present, for pyridoxine and pantothenic acid. This select group of fundamental water-soluble metabolic catalysts will probably extend in time to include biotin and one or two other previously mentioned compounds, but the most useful and important ones are already in our hands.

Someone has remarked that "It is the intuition of unity amid diversity which impels science." This well-phrased truth was almost undoubtedly not inspired by early work on the vitamin B complex, but might have been so inspired in recent years when the unity of occurrence, distribution and function of the B complex in nature has become increasingly apparent.

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Book Reviews

The Ring Index, by AUSTIN M. PATTERSON and LEONARD T. CAPELL. 661 pages. 6 x 9. 1940. New York: Reinhold Publ. Corp. $8.00.

This is a catalog of 3978 ring compounds compiled by the author for the purpose of systematizing and classifying the ring systems. Each compound is illustrated with a structural formula, its name and at least one reference to the chemical literature. The systems are classified according to the number of rings. A subclassification shows if the ring is carbocyclic or heterocyclic, fused, bridged or spiro. The volume represents work done over approximately twenty years and it is believed that it will be found to be a valuable addition to every chemical library.—A. G. D.

The Life of Ira Remsen, by FREDERICK H. GETMAN. 172 pages. $6^1/_8$ x $9^1/_4$. 1940. Easton, Pa.: Journal of Chemical Education. $2.50.

This little volume is an interesting sketch of the life of Ira Remsen who lived during the period in which chemistry as a science was building up in this country. Ira Remsen, chemist, professor and college president, was schooled in Germany under Liebig, Volhard, Fittig and Wöhler. He was one of the first in this country to appreciate the value of laboratory instruction in chemistry and during his long sojourn at Johns Hopkins as professor and president, he saw that institution rise to a position of one of the foremost among education institutions in the country. The book is full of inspiration and is worth reading.—A. G. D.

Photodynamic Action and Diseases Caused by Light, by HAROLD FRANCIS BLUM. A. C. S. Monograph 85. 309 pages. 1941. New York: Reinhold Publishing Corp. $6.00.

This volume is a critical study of the rather extensive literature on photodynamic action and its relation to certain diseases of man and animals. It begins with a brief, but clear introduction on the nature of radiation and its biological effects. The succeeding section discusses photodynamic action in which consideration is given to the factors determining photodynamic effectiveness and their bearing on the theory proposed. Part III, which deals with the diseases produced by light in animals, gives an interesting account of hypericism, geeldikkop and fagopyrism. Part IV discusses in detail the diseases produced by light in man, both those caused by abnormal sensitivity to ultraviolet radiation and those caused by sensitization to visible light. The relation of light to skin cancer is also discussed. The book represents a very complete survey of the progress which has been made in the study of photodynamic action and should be of interest to the specialist in this field primarily, also to physicians and pharmacists.—A. G. D.